PATENT SPECIFICATION 903,866

NO DRAWINGS.

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Date of Application and filing Complete Specification:
May 9, 1961. *No. 16874/61.*

Complete Specification Published: Aug. 22, 1962.

Index at Acceptance:—Class 81(1), B2(C:H:S), B2(C:H:S).

International Classification:—A61k.

COMPLETE SPECIFICATION.

Therapeutic Preparations Containing 7-Substituted Theophylline Derivatives.

We, LES LABORATOIRES DAUSSE, a French Body Corporate, of 4 rue Aubriot, Paris, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to therapeutic preparations containing 7-substituted theophylline derivatives.

According to the present invention there is provided a therapeutic composition of matter comprising (a) a purine component having a musculotropic action which is a water-soluble, 7-substituted theophylline derivative, such as 7 - β - hydroxy - ethyl theophylline, 7-β - γ - dihydroxypropyl theophylline and salts of theophylline - 7 - ethanoic acid; and (b) an adrenergic component which is the hydrochloride of 1 - (3 : 4 - dihydroxyphenyl)-2-methylamino-1-propanol.

It has been found that a medicinal synergy exists between the hydrochloride of 1-(3 : 4-dihydroxyphenyl) - 2 - methylamino - 1 - propanol and the purine components as hereinbefore defined.

The potentiated bronchodilatory effect obtained by the administration of the composition - containing 1 - (3 : 4 - dihydroxy, phenyl) - 2 - methylamino - 1 - propanol, acting by means of an adrenergic mechanism, and the above-defined purine components, of which the action is mainly musculotropic, are particularly useful in the treatment of bronchial dyspnea and more especially asthma.

This potentiation has been shown by the method of recording the tonus of the bronchi of the guinea pig as described by Halpern (Arch. Int. Pharmacodyn. et Therap., 1942, 68, 339).

The minimum active doses A and P of the adrenergic component and of the purine component on acetylcholinic bronchospasm having been determined, doses A^1 and P^1 of each of these components, lower than the doses A and P respectively, are chosen, and it is found that they have no action on the bronchospasm produced by the injection of acetylcholine.

Continuing the experiment, there are simultaneously administered to the guinea pig the dose A^1 of adrenergic component and the dose P^1 of purine component, and it is found that this association is capable of inhibiting and sometimes even suppressing the bronchospasm produced by acetylcholine, the latter being employed in the same dose throughout the experiment.

Thus, the simultaneous administration of an ineffective does A^1 of the hydrochloride of 1 - (3 : 4 - dihydroxyphenyl) - 2 - methylamino-1-propanol and of an ineffective dose P^1 of a purine component, or of a mixture of purine components, produces by mutual potentiation an unexpected bronchodilatory effect, since it is greater than the sum of the effects peculiar to each of the constituents of the composition.

The new synergic compositions have many advantages.

In the first place they permit of obtaining a considerable bronchodilatory effect by utilising only small quantities of the substances constituting the composition. Thus, the desired therapeutic effect can be fully obtained despite the reduction of the posology of each of the constituents, which results in a

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lowering of the toxicity without a diminution of the activity.

For example, it is known that adrenergic substances, of which 1-(3 : 4-dihydroxphenyl)-2 - methylamino - 1 - propanol hydrochloride is one, produce fairly frequently tachycardia and signs of central excitation which result in trembling of the extremities, notably of the hands, and insomnia.

The synergic action of the purine bases makes it possible to reduce the dose of 1-(3 : 4 - dihydroxyphenyl) - 2 - methylamino-1-propanol and to reduce to a very considerable extent, or to eliminate, the secondary effects in question.

Since the purine bases also have central stimulating effects characterised essentially by insomnia, it is desirable to add to the synergic compositions of the present invention a quantity of a drug which is a barbituric derivative. Butobarbital or butylethylmalonylurea has proved particularly desirable from this standpoint.

The compositions may comprise in addition one or more other purine substances selected from theophylline, theophylline ethylenediamine and caffeine.

The new compositions are of value in the treatment of respiratory troubles of bronchial or pulmonary origin, of asthma, of pulmonary emphysema, of chronic bronchitis, of pulmonary sclerosis, of chronic catarrh of the respiratory passages and of silicosis.

The purine component and the adrenergic component may be associated with an excipient for suppositories, an aqueous excipient for parenteral administration, an aqueous excipient for administration by the aerial route or an excipient for oral administration.

When the composition is used in an aqueous medium, it is desirable to take account of the tendency of the diphenol, which is 1-(3 : 4-dihydroxyphenyl) - 2 - methylamino - 1 - propanol, to oxidise in the presence of compounds having an alkaline reaction. It is therefore important to avoid the choice of a theophylline derivative having an alkaline reaction and it is preferred that there should be included in the aqueous medium an antioxidant or a reducing agent which is acceptable from the pharmacological viewpoint, for example sodium bisulphite or sodium formaldehyde sulphoxylate.

Examples of pharmaceutical forms of the compositions of the present invention are the following :—

EXAMPLE I.

Parenteral Administration :—

(1) 1 - (3 : 4 - Dihydroxyphenyl) - 2 - methylamino 1-propanol hydrochloride .. 0.025 g.
7 - β - γ - Dihydroxypropyl theophylline .. .. 2.50 g.
Reducing solvent q.s. .. 50 ml.

(2) 1 - (3 : 4 - Dihydroxyphenyl) - 2 - methylamino - 1-propanol hydrochloride .. 0.025 g.
7 - β - γ - Dihydroxypropyl theophylline .. .. 4 g.
Reducing solvent q.s. .. 50 ml.

In both cases, the reducing solvent employed is a solution of the following composition :—

Sodium bisulphite solution ..	2.5 ml.
Disodium sulphite	0.50 g.
Distilled water q.s.	1000 ml.

It is to be noted that these solutions can be distributed in 1 ml. or 2 ml. ampoules, so that there are obtained either ampoules containing ½ mg. or ampoules containing 1 mg. of 1 - (3 : 4 - dihydroxyphenyl) - 2 - methylamino-1-propanol hydrochloride.

These ampoules (preferably those of 1 ml. containing only ½ mg. of 1-(3 : 4-dihydroxyphenyl) - 2 - methylamino - 1 - propanol hydrochloride) may be used for shallow subcutaneous or intramuscular injections.

EXAMPLE II.

Aqueous solution for atomisation :—

(1) Ampoule A

1 - (3 : 4 - Dihydroxyphenyl) - 2 - methylamino - 1-propanol hydrochloride ..	0.01 g.
Monosodium sulphite solution	0.003 ml.
Distilled water q.s. ..	1 ml.

Ampoule B

7 - β - γ - Dihydroxypropyl theophylline	0.375 g.
Distilled water q.s. ..	10 ml.

The contents of the two ampoules are mixed and the mixture administered in aerosol form by discharge from a pressurised container.

(2) The following single solution compositions may also be adopted, the reducing solvent being that which is specified for solutions intended for parenteral administration.

1 - (3 : 4 - dihydroxyphenyl) - 2-methylamino - 1 - propanol hydrochloride	0.01 g.
7 - β - γ - Dihydroxypropyl theophylline	0.30 g.
Reducing solvent q.s.	10 ml.

EXAMPLE III.

Suppositories :—

(1) For adults :—

1 - (3 : 4 - Dihydroxyphenyl) - 2 - methylamino - 1-propanol hydrochloride ..	0.005 g.
7 - β - γ - Dihydroxypropyl theophylline	0.30 g.
Sodium hydrosulphite ..	0.002 g.
Eutectic mixture of glycerides of fatty acids of natural vegetable origin (m.p. + 35° C.)	1.655 g.

(2) For infants :—

1 - (3 : 4 - Dihydroxyphenyl) - 2 - methylamino - 1-propanol hydrochloride ..	0.0015 g.
7 - β - γ - Dihydroxypropyl theophylline	0.085 g.
Sodium hydrosulphite ..	0.0019 g.
Cochineal carmine ..	0.0004 g.
Eutectic mixture of glycerides of fatty acids of natural vegetable origin (m.p. + 35° C.)	1.800 g.

(3) With butobarbital :—

1 - (3 : 4 - Dihydroxyphenyl) - 2 - methylamino - 1-propanol hydrochloride ..	0.005 g.
7 - β - γ - Dihydroxypropyl theophylline	0.30 g.
Butobarbital	0.05 g.
Sodium hydrosulphite ..	0.002 g.
Eutectic mixture of glycerides of fatty acids of natural vegetable origin (m.p. + 35° C.)	1.605 g.

EXAMPLE IV.

Tablets :—

7 - β - γ - Dihydroxypropyl theophylline	0.04 g.	Nucleus : 0.20 g.
Caffeine	0.06 g.	
1 - (3 : 4 - Dihydroxyphenyl - 2 - methylamino - 1 - propanol hydrochloride	0.01 g.	
Icing sugar	0.02 g.	
Maize starch ..	0.01 g.	
Potato starch ..	0.0125 g.	
Paraffin oil	0.002 g.	
Talcum	0.0455 g.	
Lac varnish ..	0.005 g.	
Absorbent powder ..	0.005 g.	
Talcum	0.02 g.	
Crystallised sugar ..	0.13 g.	
Erythrosin	traces	
Carnauba wax ..	traces	

WHAT WE CLAIM IS :—

1. A therapeutic composition of matter comprising (a) a purine component having a musculotropic action which is a water-soluble 7-substituted theophylline derivative; and (b) an adrenergic component which is the hydrochloride of 1-(3 : 4-dihydroxyphenyl) - 2 - methylamino - 1 - propanol.

2. A composition according to Claim 1 wherein the theophylline derivative is 7-β-hydroxyethyl theophylline, 7-β-γ-dihydroxypropyl theophylline or a salt of theophylline-7-ethanoic acid.

3. A composition according to Claim 1 or 2 wherein the purine component and the adrenergic component are associated with an excipient for suppositories, an aqueous excipient for parenteral administration, an aqueous excipient for administration by the aerial route or an excipient for oral administration.

4. A composition according to Claim 3 wherein the excipient contains a pharmacologically acceptable antioxidant or reducing agent.

5. A composition according to any of Claims 1—4 which contains in addition a drug which is a barbituric acid derivative.

6. A composition according to Claim 5 which contains butobarbital.

7. A composition according to any of Claims 1—6 which further contains one or more other purine substances selected from theophylline, theophylline ethylenediamine and caffeine.

8. A therapeutic composition of matter according to Claim 1 substantially as hereinbefore described with reference to any of the foregoing specific examples.

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Abingdon : Printed for Her Majesty's Stationery Office, by Burgess & Son (Abingdon), Ltd.—1962.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2,
from which copies may be obtained.